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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,894	04/27/2001	Lu-Kwang Ju	UA-338	5277

7590 10/01/2004

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EXAMINER
MARX, IRENE

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,894	JU, LU-KWANG	
	Examiner	Art Unit	
	Irene Marx	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-34-71* is/are pending in the application.

4a) Of the above claim(s) *35-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-34 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/30/04 has been entered.

Claims 1-4, 6-34 and 71 are being considered on the merits. Claims 35-70 are withdrawn from consideration as directed to a non-elected invention.

The amendment presented fails to comply with the Revised Amendment Format 37 CFR 1.121. Claim 35 is indicated as "original" rather than "withdrawn". Correction is **required**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-34 and 71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No basis or support is found in the present specification for the use of microorganisms that "alternately" use of oxygen and an alternative oxidant source other than oxygen for cellular respiration. In American Heritage® Dictionary the definition of "alternate" is : To do, use, or occur in successive turns, to interchange, rotate. This is not the material presented in the as filed specification, wherein no mention is made of alternating the oxidant sources or how to achieve this alternation. The "selection" process required to obtain such a microorganism is not clearly delineated in the instant written disclosure. In addition, it is uncertain how "an alternative oxidant" is identified for any and all microorganisms, the nature of which is not determined. It is also uncertain how a microorganism is to be selected that is capable of readily switching at will between alternative oxidant sources in order to alternate them..

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-4, 6-34 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "selection" process used is not clearly delineated in claim 1. In addition, it is uncertain how "an alternative oxidant" is identified for any and all microorganisms, the nature of which is not determined. It is also uncertain how a microorganism is to be selected that is capable of readily switching at will between alternative oxidant sources in order to alternate them as now claim designated.

Claims 1-4, 6-34 and 71 are incomplete in the absence of a recovery step for the product produced.

While there is no specific rule or statutory requirement which specifically addresses the need for a recovery step in a process of preparing a composition, it is clear from the record and would be expected from conventional preparation processes that the product must be isolated or recovered. Thus, the claims fail to particularly point out and distinctly claim the "complete" process since the recovery step is missing from the claims. The metes and bounds of the claimed process are therefore not clearly established or delineated.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicant's argument that a microorganism is selected based on the knowledge that it is capable of producing a desired biological product is noted. However, the claim designated invention requires the selection to be based on utilization of oxygen or an alternative oxidant source. With regard to the "desire" to form a product, it is unclear how one of ordinary skill in the art is to determine what is desired. This term is ambiguous and open to interpretation. The information in the as-filed specification is not specific or particular regarding methodology or protocol to be used in the selection process and is limited to the use of *Pseudomonas aeruginosa* and the production of rhamnolipids as the "desired" product. The broad laundry lists of microorganisms as well as the broad laundry lists of products is not informative of the specific protocol required to screen for the capability of production of a particular desired product.

The rejection is deemed proper and it is adhered to

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 10, 16 and 71 are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Varma *et al.* for the reasons as stated in the last Office action and the further reasons below..

The claims are directed to the production of a biological product with a microorganism which includes bacteria, yeasts, molds and archaea in the presence of an alternative oxidant source under aerobic conditions such that the strain may utilize the alternative oxidant source.

Varma *et al.* disclose the production of cells of the microorganism *E. coli* in the presence of the alternative oxidant source acetate or fumarate under aerobic conditions such that the strain uses the alternative oxidant source. See, e.g., page 3730, col. 2, paragraph 4 et seq.. At some point during the process the microorganism will alternate between the two oxidant sources.

Claim 71 is included in the rejection to the extent that the claim merely mentions "defined medium" in the preamble. A defined medium does not appear to be used in the process.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Counsel argues that Varma *et al.* suggest that cometabolization of glucose and acetate was observed. In this regard, counsel baldly argues that a carbon source for metabolization is different from a carbon source for "cellular respiration". However, the arguments by counsel have not been substantiated with appropriate evidence. It is well settled that arguments by counsel do not constitute evidence. Metabolism is a broader term that encompasses respiration, since it pertains to all of the enzyme-catalyzed transformation of organic molecules in living cells, while respiration pertains to the oxidative breakdown and release of energy from nutrient molecules by reaction with oxygen, for example. Metabolism requires respiration for the release of energy to sustain life.. It is unclear how applicant intends to isolate the process of cellular respiration from metabolism with respect to a given carbon source. Production of energy is an integral part of metabolism.

There is nothing in the invention as claimed requiring that a specific material added to the culture medium. And, even if it did, the process of production of an intermediate biological product by a microorganisms would comprise the same steps of aerobic metabolism or respiration steps followed by anaerobic metabolism or respiration and have the identical effect.

In addition, counsel asserts that since Varma *et al.* does not explicitly recite that a suitable pH is maintained it is improper to infer that this is the case. However, the reference clearly teaches that the pH used is "suitable" to produce the desired product or products. Therefore, it is clear that the pH is "maintained" in the context of the process as claimed which does not specify specific levels and time-frames for this "maintaining". Therefore, the invention as claimed reads on the reference.

Therefore the rejection is deemed proper and it is adhered to.

Claims 1-4, 6, 10, 13, 15, 17-20, 22, 27-29, 31-34 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Giani *et al.* for the reasons as stated in the last Office action and the further reasons below.

The claims are directed to the production of a biological product with a microorganism including bacteria, yeasts, molds and archaea in the presence of an alternative oxidant source under aerobic conditions such that the strain may utilize the alternative oxidant source.

Giani *et al.* disclose the production of cells of the microorganism *Pseudomonas aeruginosa* in the presence of the alternative oxidant source $NaNO_3$ under aerobic conditions such that at least a portion of the cells uses the alternative oxidant source when the maximum oxygen supply is less than the cells' oxygen requirements.. See, e.g., col. 5, lines 25-67 and Example 1.

Claim 71 is included in the rejection to the extent that the claim merely mentions "defined medium" in the preamble. A defined medium does not appear to be used in the process.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

The basis for Applicants' allegation that the reference does not teach maintaining the culture medium at a desired pH is unclear, inasmuch as no specific level and no particular time-frame are claim designated.

Similarly, applicant has not established with appropriate evidence that the amount of alternative oxidant provided is insufficient for cellular respiration. As long as the material is in the culture medium it will be used by the microorganism even though it was provided for a different purpose. That if the demand for oxygen exceeds the available oxygen, Giani indicates that the aeration rate can be increased does not necessarily mean that demand never exceeds oxygen availability. However, a careful reading of the claim as written will show that it does not require oxygen demand to exceed oxygen availability at any point. In any event, should the oxygen requirement for cellular respiration of the microorganism within the culture medium be greater than the maximum rate of oxygen supply to the culture medium, then only a portion of the microorganism concentration within the culture medium is required to utilize the alternative oxidant source for cellular respiration. This reads on a cell or two.

Therefore the rejection is deemed proper and it is adhered to.

Claims 1-4, 6-34 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wendt *et al.* taken with Brock and Wagner *et al.*.

The claims are directed to the production of a biological product with a microorganism including bacteria, yeasts, molds and archea in the presence of an alternative oxidant source under aerobic conditions such that the strain may utilize the alternative oxidant source under anaerobic conditions.

Wendt *et al.* disclose a process for the production of a biological product with cells of a microorganism including *Pseudomonas* (col. 4, lines 58-64) under aerobic and anaerobic conditions in the presence of alternative oxidant sources such as nitrates such that the strain uses the alternative oxidant source when the demand of oxygen exceeds the supply. See, e.g., col. 6, lines 27-60.

The reference differs from the claimed invention in that nitrate is the only oxidant or electron acceptor disclosed for anaerobic respiration. However, Brock discloses a variety of such oxidants, including fumarate, sulfate, sulfur, ferric ion and nitrite (See, e.g., pages 113-114).

The substitution of nitrate or another ion with of salts or acids as the source of the respective ion is deemed to be well within the ordinary skill in the art, particularly since the respective ions are generally provided as a salt in an aqueous nutrient medium environment.

The references further differ from the invention as claimed in the use of small acids or fatty acids in the medium. However, Wagner *et al.* adequately demonstrate that it is routine in the art to provide nutrient media containing small acids, such as malonate, succinate, pyruvate or malate, or fatty acids such as stearic acid for microorganisms, including *Pseudomonas.* (See, e.g., col. 3). The Wagner *et al.* reference also addresses the use of nutrient limitation in the cultivation of bacteria, specifically by limiting magnesium or nitrogen for the production of rhamnolipids with *Pseudomonas* (See, e.g., Examples 2-3).

One of ordinary skill in the art would have had a reasonable expectation of success in obtaining a biological product by cultivation of a microorganism in the presence of an alternative oxidant source under aerobic conditions followed by anaerobic conditions using a variety of carbon sources and the limitation of a variety of nutrients to boost yields of a desired product depending on the specific microorganism to be cultured and/or the product to be produced.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of cultivation of Wendt *et al.* by the substitution of nitrate by other oxidants, as suggested by Brock, when the oxygen demand exceeds the oxygen supply, as well as the use of nutrient limitation and various carbon substrates, as suggested by the teachings of Wagner *et al.* for the expected benefit of maximizing the production of useful biological products produced by a microorganism suitable for use in the pharmaceutical industries and for foods or feed, for example.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1-4, 6-34 and 71 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Giani *et al.* taken with Brock and Wagner *et al.* for the reasons as stated in the last Office action and the further reasons below.

The claims are directed to the production of a biological product with a microorganism including bacteria, yeasts, molds and archaea in the presence of an alternative oxidant source under aerobic conditions such that the strain may utilize the alternative oxidant source.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

A noted *supra,* applicant has not established with appropriate evidence that the amount of alternative oxidant provided is insufficient for cellular respiration when the oxygen requirements for cellular respiration are greater than the maximum rate of oxygen supply to the culture medium. As long as some quantity of sodium nitrate is in the culture medium, at least a few cells of *Pseudomonas aeruginosa* will use this material when oxygen demand exceeds supply, even though it was provided for a different purpose. The use of sodium nitrate is an intrinsic property of *Pseudomonas aeruginosa* for this purpose. This basic principle of metabolism of *Pseudomonas aeruginosa* is not altered by the fact that Giani indicates that the aeration rate can be increased when oxygen demand exceeds supply. The reference does not categorically state that this is always the case.

In addition, a careful reading of the claim as written will show that there is no requirement for the oxygen demand to exceed oxygen availability at any point. In any event, should the oxygen requirement for cellular respiration of the microorganism within the culture medium be greater than the maximum rate of oxygen supply to the culture medium, then only a portion of the microorganism concentration within the culture medium is required to utilize the alternative oxidant source for cellular respiration. A portion reads on a cell or two.

Applicant argues that one of the objects of the present invention is to specifically avoid the use of antifoaming agents. However, this is irrelevant to the invention as claimed which is directed to the production of any product with any microorganism under any conditions. Only claims 7-8 require *Pseudomonas* and claim 9 requires *P. aeruginosa.* Claim 6 includes a laundry list of microorganisms. That the present invention seeks to avoid the use of an antifoaming agent is not part of the broadly claimed invention. Applicant appears to rely on the

example for this statement. However, the example is directed to the production of rhamnolipids with an unidentified strain of *P. aeruginosa* with the addition of specific amounts of sodium nitrate (Specification, pages 19-20). There is no clear correlation between this material and the invention as claimed.

Applicant appears to wish to extrapolate results pertaining to a specific fermentation process using a strain *P. aeruginosa* to claim a process broadly. However, the process as claimed does not distinguish over the prior art processes providing an alternative oxidant source.

With respect to applicant's criticism that the combination of references would change the principle of operation of the prior art, it is noted that even though the process of Giani *et al.* may not disclose all of the metabolic processes, principles of operation and ramifications of supplying an alternative oxidant to the culture, the claimed process is substantially taught by the reference. Moreover, as noted *supra,* a careful reading of the claim as written shows that the claimed invention does not require oxygen demand to exceed oxygen availability at any point. In any event, should the oxygen requirement for cellular respiration of the microorganism within the culture medium be greater than the maximum rate of oxygen supply to the culture medium, then only a portion of the microorganism concentration within the culture medium is required to utilize the alternative oxidant source for cellular respiration. This reads on a cell or two.

Brock is cited to demonstrate that many alternative oxidants are known in the art, such as fumarate, sulfate, sulfur, ferric ion and nitrite (See, e.g., pages 113-114). Wagner is cited to demonstrate that various substrates including small acids, such as malonate, succinate, pyruvate or malate, or fatty acids such as stearic acid are routinely used in this art in media for microorganisms, including *Pseudomonas.* (See, e.g., col. 3). In addition, Wagner *et al.* was cited to demonstrate the routine use of nutrient limitation in the cultivation of bacteria, specifically by limiting magnesium or nitrogen for the production of rhamnolipids with *Pseudomonas* (See, e.g., Examples 2-3).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to modify the process of cultivation of Giani *et al.* wherein an alternative oxidant is supplied, by the substitution of nitrate by other oxidants, as suggested by Brock as well as the use of expedients such as nutrient limitation and

various carbon substrates, as suggested by the teachings of Wagner *et al.* for the expected benefit of maximizing the production of useful biological products produced by microorganisms suitable for the pharmaceutical industries and for foods or feed, for example.

Therefore the rejection is deemed proper and it is adhered to.
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (571) 272-0919. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0926.

Irene Marx
Primary Examiner
Art Unit 1651